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10/567,407	11/13/2006	Arthur M. Deboeck	2505-017	9466

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EXAMINER	
WESTERBERG, NISSA M	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,407	DEBOECK ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/6/06, 11/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: figures are present in the specification. Graphical illustrations do not come within the purview of 37 CFR 1.58(a). See MPEP 608.01 VI for more information.

Appropriate correction by submission of drawings in accordance with 37 CFR 1.81 is required.

Claim Objections

2. Claim 20 is objected to because of the following informalities: there appears to be a typographical error present in the phrase “vitamine B12”. Appropriate correction is required.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1 – 17, 19 and 21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12 and 13 of U.S. Patent No. 5,545,628 in view of Dierkes et al. (DE 19910682) and Serfontein (EP 0595005).

The claims of the instant application recite a unit form comprising fenofibrate and a homocysteine lowering agent such as folic acid, vitamin B12, vitamin B6 and/or betaine wherein the homocysteine lowering agent composition is a modified release form. Polyglyceride(s) and micronized fenofibrate may be present in the unit form.

The claims of '628 recite composition comprising fenofibrate and one or more polyglycolyzed glycerides.

Dierkes et al. discloses a combination of active ingredients as a therapy for hyperlipoproteinenia (p 2, ¶ 1) which comprise a fibrate and one or more of cobalamin (vitamin B12), folic acid, vitamin B6 (pyridoxine), betaine and N-acetyl cysteine (p 4, ¶ 4 – p 5, ¶1).

Serfontein discloses a preparation for the lowering of homocysteine levels which comprise vitamins B6 and B12 and folic acid (abstract) in which preferably, the vitamin B6 and folate or precursor thereof are designed to release the active ingredient over a period of at least 2 hours (p 6, ln 6 – 7). Particularly for pyridoxine (vitamin B6), delayed release can alleviate problems with the limited capacity of the liver to convert pyridoxine into pyridoxal phosphate (PLP) and the resulting poor utilization and undesirable entry of pyroxidine into peripheral cells and erthryocytes (p 5, ln 4 – 8).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to add vitamin derivatives such as vitamin B12, B6 or folic acid to the fenofibrate/polyglyceride composition recited in the claims of '628 as such compositions are taught by Dierkes et al. The artisan of ordinary skill would have also provided the vitamin derivative component as a modified release formulation as Serfontein teaches

that delayed release of vitamin B6 in particular results in better utilization of the active ingredient by the body. That composition is the composition recited in the claims of the instant invention.

5. Claims 1 – 17, 19 and 21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 – 9, 12 – 14, 18, 19, 30, 40, 42 – 45 and 52 – 54 of copending Application No. 11/347822 in view of Serfontein (EP 0595005).

The claims of the instant application recite a unit form comprising fenofibrate and a homocysteine lowering agent such as folic acid, vitamin B12, vitamin B6 and/or betaine wherein the homocysteine lowering agent composition is a modified release form. Polyglyceride(s) and micronized fenofibrate may be present in the unit form.

The claims of '822 recite a controlled release composition of pravastatin and fenofibrate that can further include vitamin derivatives such as folic acid, vitamin B6 or vitamin B12 (such as in claim 4).

The claims of '822 do not recite the release profile of the vitamin derivative component.

Serfontein discloses a preparation for the lowering of homocysteine levels which comprise vitamins B6 and B12 and folic acid (abstract) in which preferably, the vitamin B6 and folate or precursor thereof are designed to release the active ingredient over a period of at least 2 hours (p 6, ln 6 – 7). Particularly for pyridoxine (vitamin B6), delayed release can alleviate problems with the limited capacity of the liver to convert pyridoxine

into pyridoxal phosphate (PLP) and the resulting poor utilization and undesirable entry of pyroxidine into peripheral cells and erthryocytes (p 5, ln 4 – 8).

It would have been obvious to one of ordinary skill in the art to prepare the pravastatin/fenofibrat/vitamin derivative composition recited in the claims of '822 and provide the vitamin derivative component in a modified release formulation as Serfontein teaches that delayed release of vitamin B6 results in better utilization of the active ingredient by the body. That composition is the composition recited in the claims of the instant invention.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4 – 7, 9 – 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a "homocysteine lowering agent". In the specification and claims, folic acid, vitamin B12, vitamin B6 and betaine are explicitly identified as homocysteine lowering agents.

These four compounds exemplified are diverse in structure and the specification provides insufficient written description to support the genus of "homocysteine lowering compounds" encompassed by the claim.

8. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. None of the fibrate derivatives other than fenofibrate meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus of derivatives encompassed by the claim, since there is no description of the structural relationship of these derivatives provided in the specification and Applicant has not provided a description as to how the base molecule may be changed while remaining a derivative.

Claim Rejections - 35 USC § 112 2nd Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 4 recites the broad recitation of 25 mg to 400 mg, and the claim also recites 50 mg to 300 mg which is the narrower statement of the range.

11. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially immediate release" is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim,

the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the scope of the invention. How immediate the release of the first composition or how long of a delay in the release is permitted but will still remain a "substantially immediate release profile" is not defined so an artisan of skill in the art would not be apprised of the metes and bounds of the instant claim.

12. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 15

recites the broad recitation of between 1 and 10 hours, and the claim also recites ranges of 3 and 8 as well as 2 and 6 hours, which are narrower statements of the range.

13. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially free of fibrate derivative" is a relative term which renders the claim indefinite. The term "substantially free" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. How much of the fibrate derivative allowed to present in the second composition is not defined so an artisan of skill in the art would not be apprised of the metes and bounds of the instant claim. It is also unclear from claim 19 if the two components are required to be completely separate dosage forms so that the unit dose comprises, for example, a fenofibrate capsule and a separate homocysteine-lowering agent tablet or if the limitations of this claim are met when the two different components are present as separate zones or layers of a single tablet or capsule.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1 – 4 and 7 – 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dierkes et al. (English translation of DE19910682) in view of Serfontein (EP 0595005).

Dierkes et al. discloses a combination of active ingredients as a therapy for hyperlipoproteinenia (p 2, ¶ 1) which comprise a combination of fibrates and one or

more of cobalamin (vitamin B12), folic acid, vitamin B6 (pyridoxine), betaine and N-acetyl cysteine (p 4, ¶ 4 – p 5, ¶1). The combination of fibrate with vitamins is preferably administered orally in forms such as dragees or film tablets (p 6, ¶ 1). In example 1, a dragee containing 200 mg fenofibrate and 2.1 mg total of homocysteine lowering agents (pteroylglutamic (folic) acid and pyridoxine chloride) is prepared.

Dierkes et al. does not disclose the release profile of the active ingredients.

Serfontein discloses a preparation for the lowering of homocysteine levels which comprise vitamins B6 and B12 and folic acid (abstract) in which preferably, the vitamin B6 and folate or precursor thereof are designed to release the active ingredient over a period of at least 2 hours (p 6, ln 6 – 7). Particularly for pyridoxine (vitamin B6), delayed release can alleviate problems with the limited capacity of the liver to convert pyridoxine into pyridoxal phosphate (PLP) and the resulting poor utilization and undesirable entry of pyroxidine into peripheral cells and erthryocytes (p 5, ln 4 – 8). The active ingredients can be provided separately in separate distinctive dosage forms such as capsules, tablets or coated tablets which can be combined in a single package (p 5, ln 57 – p 6, ln 3). Due to the varying absorption rates of the various components, a composite plaster with 3 zones, each with one active ingredient and excipients can be prepared (col 7, ln 51 – 58).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to take the formulation of fenofribrate and the homocysteine lowering agents vitamin B6, vitamin B12, folic acid and/or betaine taught by Dierkes et al. and to prepare the composition in such a manner that the vitamin B6 and/or folic acid exhibit a

modified release profile in which those ingredients are released over a time period of at least 2 hours, taught by Serfontein to decrease unwanted side effects caused by the ability of the liver to process vitamin B6. As Dierkes et al. does not disclose the inclusion on any materials that would retard the release of the fenofibrate or any other of the active ingredients, the fenofibrate release of Dierkes is an immediate release composition. Serfontein also teaches that the dosage form can contain different 'zones' each containing only one active ingredient, free of the other active ingredients, to accommodate the different release profiles that are optimal for each ingredient. Alternatively, the active ingredients can also be in physically separate tablets or capsule.

The dissolution rate and T_{max} of the delayed release elements of the homocysteine lowering agents are not disclosed by Serfontein, although a release over at least 2 hours is disclosed. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

18. Claims 1 – 17, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dierkes et al. and Serfontein as applied to claims 1 – 4, 7 – 17, 19 and 21 above, and further in view of Deboeck et al. (US 5,545,628).

Dierkes et al. and Serfontein disclose a combination of a fibrate such as fenofibrate with vitamins such as B6, B12 and folic acid or betaine where the release of the vitamin B6 and/or folic acid is spread out over time.

Neither reference discloses the use of micronized fenofibrate or the inclusion of at least one polyglyceride.

Deboeck et al. discloses that fenofibrate can be micronized with a solid wetting agent and significantly increases the bioavailability of the fenofibrate (col 1, ln 46 – 61). Alternatively, the bioavailability of the fenofibrate can be improved to the same extent as micronization by the inclusion of a polyglycolized glyceride in the formulation (col 2, ln 21 – 25). In the example, the polyglycerol GELUCIRE® 44/12 is used (col 3, ln 15 – 17; col 4, ln 31 – 35).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare the combination of fenofibrate and homocysteine lowering agents, with a modified release of at least some of the homocysteine lowering agents as taught by Dierkes et al. and Serfontein, and to micronize the fenofribate and include a polyglyceride, both of which enhance the bioavailability of the fenofibrate component, as taught by Deboeck et al.

19. Claims 1 – 4 and 17 – 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dierkes et al. and Serfontein as applied to claims 1 – 4, 7 – 17, 19 and 21 above, and further in view of Gohel et al. (J Controlled Release 2002).

Dierkes et al. and Serfontein disclose a combination of a fibrate such as fenofibrate with vitamins such as B6, B12 and folic acid or betaine. The various components may be in separate tablet or capsules, or present in the same unit dosage form but within different zones to accommodate the different optimal release profiles of the different active ingredients.

Neither reference discloses a single unit in which a tablet with the homocysteine lowering agent and a paste with the fibrate derivative are placed inside a capsule as the final dosage form.

Gohel et al. discloses the modulation of the release of active ingredient release over time by the use capsule delivery system that contains a powder plug (paste) which can contain active ingredient, and a tablet plug which can also contain active ingredient (p 159, col 1, Section 2.4). As shown in the various figures, the compositions of these two elements results in a variety of dissolution profiles and release of the active ingredient over time.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a fenofibrate dosage form with homocysteine lowering agents, at least some of which exhibit a modified release profile, as taught by Dierkes et al. and Serfontein, and to use the tablet-in-capsule formulation taught by Gohel et al. as

suitable for the programmed delivery of drugs from hard gelatin capsules using a systemic formulation approach (abstract).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8 a.m. - 4 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618
NMW